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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 9/22

A1

(11) International Publication Number: WO 87/ 00044

(43) International Publication Date: 15 January 1987 (15.01.87)

(21) International Application Number: PCT/US86/01360

(22) International Filing Date: 18 June 1986 (18.06.86)

(31) Priority Application Number: 751,125

(32) Priority Date: 2 July 1985 (02.07.85)

(33) Priority Country: US

(60) Parent Application or Grant
(63) Related by Continuation
US 751,125 (CIP)
Filed on 2 July 1985 (02.07.85)

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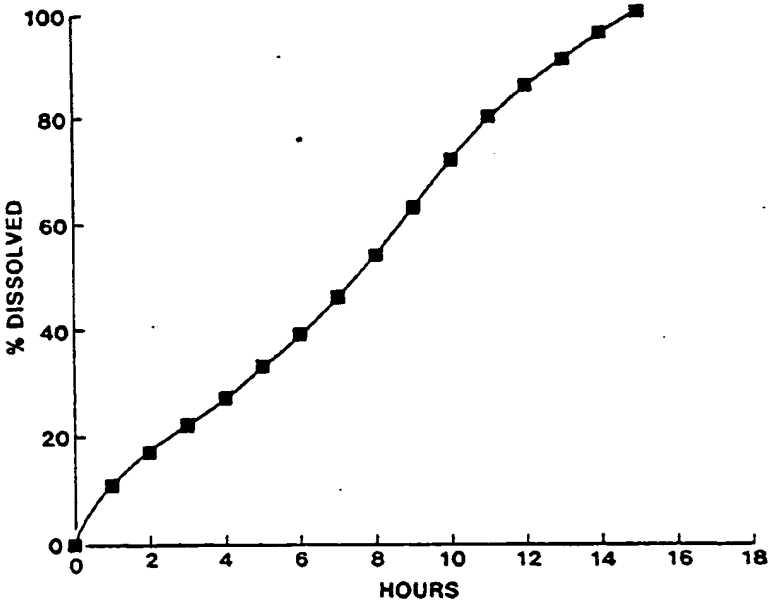
(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: THERAPEUTIC FORMULATIONS WITH BIMODAL RELEASE CHARACTERISTICS



(57) Abstract

A carrier base material to be combined with a therapeutically active medicament and formed into a solid, shaped dosage unit having a bimodal controlled release of medicament upon administration. Specifically, this invention relates to a carrier base material consisting of one or more bimodal hydroxypropylmethylcelluloses (B-HPMC's) having a physical and chemical structure which renders it suitable for use sustained release therapeutic formulations with bimodal release characteristics.

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THERAPEUTIC FORMULATIONS WITH BIMODAL RELEASE CHARACTERISTICS

BRIEF SUMMARY OF THE INVENTION

This invention relates to a carrier base material to be combined with a therapeutically active medicament and formed into a solid, shaped dosage unit having a bimodal controlled release of medicament upon administration. Specifically, this invention relates to a carrier base material consisting of one or more bimodal hydroxypropylmethylcelluloses (B-HPMC's) having a physical and chemical structure which renders it suitable for use in sustained release therapeutic formulations with bimodal release characteristics.

BACKGROUND OF THE INVENTION

The use of various hydroxypropylmethylcelluloses in carrier base materials to be combined with a therapeutically active medicament and formed into solid, shaped dosage units so as to provide a regular and prolonged release of medication upon administration is well known. See, for example, U.S. Patent Nos. 4,389,393; 4,369,172; 4,259,314; 4,357,469; 4,226,849; 3,870,790; 3,065,143; and 4,167,558.

The goal of formulators of sustained release pharmaceuticals has long been to provide a substantially constant rate of release, i.e., a zero order release rate or a drug release rate equal to the square root of time rather than a bimodal rate of release. (See FIGURES 1 and 2).

In Forest U.S. Patent 4,369,172, hydroxypropylmethylcellulose (methoxy content of 27 to 30%, hydroxypropyl content of 9 to 12%) is combined with ethylcellulose or sodium carboxymethylcellulose for prolonged release. Another Forest U.S. Patent 3,870,790 mentions a slow release buccal tablet of 80 to 100% hydroxypropylmethylcellulose (methoxy content 28 to 30%, hydroxypropyl content 7-12%) and 0 to 20% ethylcellulose. Forest U.S. patent 4,357,469 uses a hydrolyzed and oxidated hydroxypropylmethylcellulose (methoxy content 28 to 30% hydroxypropyl content 7.5 to 12%) with up to 30% ethylcellulose or 30% sodium carboxymethylcellulose. Forest German Patent DT2718-260 describes the use of a treated hydroxypropylmethylcellulose and ethylcellulose to produce a slow release formulation. Forest Patents U.S. 4,226,849 and South Africa 7,805,528 claim similar slow release formulations using hydroxypropylmethylcellulose. In U.S. Patent 3,590,117 a high viscosity grade 15,000 cps. hydroxypropylmethylcellulose is used for a sustained release

tablet that is at least 1/3 by weight hydrophilic gum. Methocels listed are E4-M, 90 HG 4,000 cps., K4-M, and K15-M. U.S. Patent 4,389,393 claims a carrier base material being one or more hydroxypropylmethylcelluloses (methoxy content 16 to 24%, hydroxypropyl content 4 to 32% and average molecular weight of at least 50,000) up to 30% by weight of a mixture of methylcellulose, sodium carboxymethylcellulose and/or other cellulose ethers. American Home Products Corp., Patent G.B. 2053-682 describes the preparation of a sugar coated sustained release tablet using hydroxypropylmethylcellulose (4,000 to 40,000 viscosity grades, 30 to 45% of total weight) in combination with ethylcellulose. Two other American Home Products Corp., U.S. Patents 4,309,405 and U.S. 4,309,406 mention a sustained release tablet using mixtures of hydroxypropylmethylcellulose in the core. Hoffman-LaRoche U.S. Patent 4,167,558 claims aspirin tablets made with mixtures of various cellulose derivatives comprised of 20 to 75% of the total tablet weight. U.S. Patent 4,259,314 describes the preparation of a slow release formulation of 80 to 95% hydroxypropylmethylcellulose (viscosity: 50-4,000 cps.) and 5 to 20% hydroxypropylcellulose. U.S. Patent 3,065,143 uses a cellulose product with a methoxyl content of 19 to 24% and hydroxypropyl content of 4 to 12%, with the HPMC comprising at least 1/3 of the total tablet weight. Sumitomo Chemical K.K. Patents J5-8135-807-A and J5-7062-224 use hydroxypropylmethylcellulose as a coating for tablets.

The effect of various METHOCEL Products on Tablet Dissolution, including F4-M, is the subject of a Dow booklet entitled "Formulating Sustained Release Pharmaceutical Products with Methocel".

Metolose 65SH-4000 has been reported to be useful as a paint thickener, as a suspending agent in spray paints, as a thickener in paint removers, as a latex stabilizer and thickener for asphalt emulsion, as a base of jelly for an external application or ointments, as a binder for cigar leaf. Metolose 65SH-1500, as a gypsum plaster additives. Metolose 65SH-400 as joint cement additive, as suspension stabilizer in vinyl chloride vinylidene polymer, as latex stabilizer, as spray paint additive, as shampoo additive to improve viscosity. Metolose 65SH-50, as suspension stabilizer in vinylchloride vinylidene polymer. Metolose 90SH-100 as suspension stabilizer in vinylchloride

vinylidene polymer, as molding binder for pencil or crayons. Metolose 90SH-15000 as cement mortar additive, as tile cement additive, as gypsum plaster additive, as plaster additive, as molding product of gypsum cement. Metolose 60SH-4000 as paint remover additive, as shampoo additive, as binder for the extrusion molding of ceramic condenser and ferrite alumina porcelains. Methocel F4-M as additive to general adhesives, dust stickers, spray stickers, caulking compounds, tile and grout adhesives, toothpastes, pie fillings, cements, creams, ointments, ophthalmic preparations, and suspensions.

DETAILED DESCRIPTION

The present invention is directed toward a carrier base material for therapeutically active medicaments in a solid dosage formulation that produces a bimodal controlled release profile characterized by a rapid initial release of medicament followed by a substantially constant rate of release for a period of time, after which the release rate is greater than the constant rate previously observed.

The advantages of the present invention, a carrier base material and bimodal controlled release formulation prepared therefrom, over conventional sustained release formulations are substantial. Conventional sustained release formulations may exhibit a zero order release profile, where the rate of release of therapeutic agent is essentially constant, or a profile in which the release rate decreases with time. As a conventional controlled release tablet moves through the gastrointestinal tract, drug absorption decreases.

An objective of the bimodal controlled release formulation of this invention is to provide for a more uniform delivery of therapeutic agent since it is now possible to increase the rate of drug release at a point when the body's ability to absorb a medicament decreases, thus providing more uniform delivery of the therapeutic agent.

Another object of the present invention is to provide a bimodal formulation giving therapeutic blood levels similar to those produced by administration of two smaller doses over an extended period of time.

The bimodal release profile of the active ingredient from the carrier of the present invention can be controlled according to the particlar therapeutic agent and its intended therapeutic effect since the initial rate of release, initial time of rate change, and the final release rate for a specific drug, are all a property of the particular

B-HPMC(s) utilized. These parameters can be selectively modified by the addition of various excipients that include, but are not limited to, non-bimodal hydroxypropylmethylcellulose (HPMC's), hydroxypropylcelluloses, lactose, starch, binders, fillers, disintegrating agents and other pharmaceutical compounding agents.

The active ingredient can be any type of therapeutic agent which lends itself to controlled release administration. Examples of such agents include antihistamines, laxatives, vitamins, decongestants, gastrointestinal sedatives, anti-inflammatory substances, antacids, anti-infectives, coronary vasodilators, cerebral vasodilators, peripheral vasodilators, psychotropics, antimanics, stimulants, antidiarrheal preparations, antianginal drugs, vasoconstrictors, anticoagulants, antithrombotic drugs, analgesics, anti-pyretics, hypnotics, sediatives, anti-emetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, anti-asthmatics, expectorants, cough suppressents, mucolytics, antiuricemic drugs, etc.

The preparation of sustained release tablets with bimodal release characteristics consists of thorough mixing of a therapeutic agent with one or more of the hydroxypropylmethylcellulose ethers of the present invention, and any other ingredients which are conventional in tablet making - such as magnesium stearate, stearic acid, Cab-O-sil(colloidal silicon dioxide) etc. Release rate modifiers, as mentioned previously, are also added at this time, if they are desired. All ingredients are mixed thoroughly. The mixture, in an amount sufficient to make a uniform batch of matrix tablets, is subjected to tableting on conventional tableting machines.

Those hydroxypropylmethylcellulose ethers effective for the present purpose are the bimodal hydroxypropylmethylcellulose ethers (B-HPMC's), with a methoxy content of 19 to 30%, a hydroxypropyoxy content of from 4 to 12%, a viscosity of from 40 to 19,000 cps, an average molecular weight of from 20,000 to 140,000, and demonstrates a bimodal release profile in accordance with the assay described in Procedure I.

Accordingly, any hydroxypropylmethylcellulose ether having the foregoing specifications, and exhibiting a bimodal release profile in

accordance with Procedure I represents a B-HPMC.

Examples of commercially available hydroxypropylmethylcellulose ethers which can be used as B-HPMC's include, but are not limited to, Metolose 65SH-50, 400, 1500 and 4000, Metolose 60SH-4000 and Metolose 90SH-100 and 15,000, all available from Shin-Etsu Ltd., Japan, as well as Methocel F4-M available from the Dow Chemical Company. Various grades of Methocel A, E and K tested do not demonstrate a bimodal release profile nor has Metolose SM-1500, a brand of methylcellulose. See, for example, the cumulative and differential plots of a 200 mg flurbiprofen/Methocel 30% K15-M of FIGURES 3 and 4.

To prepare a solid dosage formulation with bimodal release characteristics, at least one B-HPMC must be utilized. The content of the B-HPMC(s) may comprise about 5 to about 99% by weight of the total formulation, depending upon the active ingredient and length of drug release desired. The bimodal hydroxypropylmethylcelluloses (B-HPMC's) of the present invention can be optionally mixed with about 0 to 50% by weight of the total formulation of a non-bimodal hydroxypropylmethylcellulose, or methylcellulose, sodium carboxymethylcellulose or other cellulsoe ether. For example, two or more B-HPMC's, one or more non-bimodal HPMC, or other cellulose ethers in combination with one or more B-HPMC can be mixed to provide bimodal formulations of various specific release characteristics. See e.g. Example 11 and 12.

Procedure 1

Determination of Bimodal Hydroxypropylmethyl-cellulose (B-HPMC's) Utilizing Standard In Vitro Assay Procedures

The ability of hydroxypropylmethylcelluloses to produce a bimodal release profile can be readily evaluated in accordance with the following procedure.

One Hundred 300 mg Aspirin tablets are prepared from the following types and amounts of ingredients:

Aspirin	30	gm
HPMC (test material)	20.7	gm
Stearic Acid	0.881	gm
Cab-O-Sil	0.176	gm

The HPMC, aspirin, stearic acid and Cab-O-Sil are mixed thoroughly with a mechanical mixer for about 5 minutes. The mixture is tableted (Carver press, 4.8x10mm eliptical die) with a compression force of

3,500 lbs for 30 seconds.

Release rates are determined using an automated spin filter dissolution apparatus, J. Pharm. Sci. 63, 110, (1974), or other dissolution test device using the following conditions:

Media: 1,000 ml of 0.05 M phosphate buffer, pH 7.2

Temperature: 37 degrees C

Stirring Speed: 300 rpm

Spectrophotometer: Perkin-Elmer Lambda 5

Wavelength: 296 nm

Sampling Interval: 60 minutes

Release rates are plotted (cumulative and/or differential plots) and evaluated for the presence of a bimodal profile characterized by a rapid initial release of drug followed by an essentially constant rate of release for a period of time, after which the release rate is greater than the constant rate previously observed. An HPMC that produces a bimodal release rate is a B-HPMC.

For example, 300 mg aspirin tablets prepared as described above and using Metolose 65SH-4000 as the HPMC had the following percentage drug dissolved as a function of time.

Time (Hours)	% Dissolved	Rate
1	11.0	11.0
2	17.0	6.0
3	22.0	5.0
4	27.0	5.0
5	33.0	6.0
6	39.0	6.0
7	46.0	7.0
8	54.0	8.0
9	63.0	9.0
10	72.0	9.0
11	80.0	8.0
12	86.0	6.0
13	91.0	5.0
14	96.0	4.0
15	100.0	4.0
16	100.0	0.0

17	100.0	0.0
18	100.0	0.0

Cumulative and differential plots of the test data can be prepared and evaluated to more clearly illustrate the bimodal release profiles. (See FIGURES 5 and 6). Metolose 65SH-4000 is a B-HPMC.

The following methods describe the manner and process of using this invention and are to be construed as exemploary embodiments of the invention concept and not as limitations thereof.

Examples 1-3: Bimodal Controlled Release 200 mg flurbiprofen tablets containing 40% bimodal hydroxypropylmethylcellulose were prepared from the following ingredients:

Example 1:

Ingredients	mg/Tablet	Wt.%/Tablet
Flurbiprofen	200	58.0
Metolose 65SH-50	138	40.0
Stearic Acid	5.87	1.70
Cab-O-Sil	1.17	0.34

Example 2:

Flurbiprofen	200	58.0
Metolose 65SH-1500	138	40.0
Stearic Acid	5.87	1.70
Cab-O-Sil	1.17	0.34

Example 3:

Flurbiprofen	200	58.0
Metolose 65SH-4000	138	40.0
Stearic Acid	5.87	1.70
Cab-O-Sil	1.17	0.34

All ingredients are mixed for 5 min. The mixtures are then subjected to a compression force of 2,500 psi/30sec. The theoretical weight of the tablets is 345 mg. Release rates are determined, for all examples, using an automated spin-filter dissolution apparatus under the following dissolution conditions:

Media: 1,000 ml of 0.05 M phosphate buffer pH 7.20

Temperature: 37°C

Stirring Speed: 300 rpm

Sampling interval: 30 min.

Table 1 shows the percent drug dissolved per hour, and the rate of

dissolution for Examples 1-3.

Examples 4-9: Examples 4-9 show the effect of varying the amount of a bimodal hydroxypropylmethylcellulose used on 200 mg flurbiprofen formulations.

Example 4:

Ingredients	mg/Tablet	Wt.%/Tablet
Flurbiprofen	200	83.0
Metolose 90SH-100	36.2	15.0
Stearic Acid	4.10	1.70
Cab-O-Sil	0.819	0.34

Example 5:

Flurbiprofen	200	78.0
Metolose 90SH-100	51.6	20.0
Stearic Acid	4.39	1.70
Cab-O-Sil	0.877	0.34

Example 6:

Flurbiprofen	200	68.0
Metolose 90SH-100	88.2	30.0
Stearic Acid	5.00	1.70
Cab-O-Sil	1.00	0.34

Example 7:

Flurbiprofen	200	58.0
Metolose 90SH-100	138	40.0
Stearic Acid	5.87	1.70
Cab-O-Sil	1.17	0.34

Example 8:

Flurbiprofen	200	48.0
Metolose 90SH-100	209	50.0
Stearic Acid	7.09	1.70
Cab-O-Sil	1.42	0.34

Example 9:

Flurbiprofen	200	38.0
Metolose 90SH-100	316	60.0
Stearic Acid	8.96	1.70
Cab-O-Sil	1.79	0.34

Tablets are prepared and tested as stated in Examples 1-3. Tablet weight ranges from 241 mg to 527 mg. Table 2 shows the percent drug

dissolved per hour, and rate of dissolution for Examples 4-9.

Examples 10-12: Examples 10-12 show the effect of a modifying excipient, Metolose SM-1500 (methylcellulose, USP; 1500 cps), on 30 mg adinazolam mesylate formulations containing the bimodal hydroxypropylmethylcellulose, Metolose 65SH-4000.

Example 10:

Ingredients	Mg/Tablet	Wt.%/Tablet
Adinazolam mesylate	30.0	7.96
Metolose 65SH-4000	339	90.0
Stearic Acid	6.41	1.70
Cab-O-Sil (Colloidal Silicon Dixoide)	1.28	0.34

Example 11:

Adinazolam mesylate	30.0	7.96
Metolose 65SH-4000	207	55.0
Metolose SM-1500	132	35.0
Stearic Acid	6.41	1.70
Cab-O-Sil (Colloidal Silicon Dioxide)	1.28	0.34

Example 12:

Adinazolam mesylate	30.0	7.96
Metolose 65SH-4000	170.0	45.0
Metolose SM-1500	170.0	45.0
Stearic Acid	6.41	1.70
Cab-O-Sil	1.28	0.34

All ingredients are mixed for 5 min. The mixture is then subjected to a compression force of 3,500 psi/30 sec. The theoretical weight of the tablets is 377 mg. Release rates are determined as stated in Examples 1-3. Percent drug dissolved per hour and rate of dissolution are given in Table 3.

Example 13:

Ingredients	Mg/Tablet	Wt.%/Tablet
Flurbiprofen	200	64.3
Metolose 90SH-100	77.0	24.7
Metolose 90SH-4000	31.0	9.96
Stearic Acid	2.00	0.643
Cab-O-Sil (Colloidal	1.00	0.321

Silicon Dixoide)		
38-42% FD&C Yellow No. 6	0.28	0.0900

Example 14:

Flurbiprofen	200	64.3
Metolose 90SH-100	61.5	19.8
Metolose 90SH-4000	46.5	14.9
Stearic Acid	2.00	0.643
Cab-O-Sil	1.00	0.321
38-42% FD&C Yellow No. 6	0.28	0.0900

Example 15:

Flurbiprofen	200	64.3
Metolose 90SH-100	92.5	29.7
Metolose 90SH-4000	15.5	4.98
Stearic Acid	2.00	0.643
Cab-O-Sil	1.00	0.321
38-42% FD&C Yellow No. 6	0.28	0.0900

Method of Preparation:

Tablets are prepared in Examples 13, 14 and 15 by mixing flurbiprofen, metoloses, and color in a P-K blender for 5 min. The mixes are then dry granulated by slugging. The stearic acid and Cab-O-Sil are added to the dry sized granules and blended for another 5 min. Mixes are then compressed on a Beta Press. The theoretical tablet weight is 311.28 mg. Table 4 shows the percent drug dissolved versus time and the rate for the tablets.

TABLE 1

200 mg Flurbiprofen Tablets

(Hrs.) Time	Example 1 40% Metolose 65SH-50 % Dissolved	Rate	Example 2 40% Metolose 65SH-1500 %Dissolved	Rate	Example 3 40% Metolose 65SH-4000 %Dissolved	Rate
1	6.35	6.35	10.6	10.6	6.10	6.10
2	10.2	3.85	14.0	3.4	8.80	2.70
3	13.6	3.40	16.7	2.70	11.1	2.30
4	16.8	3.20	19.3	2.60	13.1	2.00
5	20.3	3.50	21.7	2.40	15.0	1.90
6	24.0	3.70	24.1	2.40	16.8	1.80
7	28.1	4.10	26.6	2.50	18.9	2.10
8	32.6	4.50	29.2	2.60	20.9	2.00
9	37.5	4.90	32.3	3.10	23.0	2.10
10	43.3	5.90	35.7	4.40	25.6	2.60
11	50.6	7.20	42.6	5.90	28.5	2.90
12	59.1	8.50	50.9	8.30	31.8	3.30
13	69.8	10.7	57.1	6.20	35.3	3.50
14	80.7	10.9	62.7	5.60	40.8	5.50
15	89.8	9.10	69.1	6.40	45.5	4.70
16	95.2	5.40	79.0	9.90	50.5	5.00
17	99.0	3.80	86.3	6.70	56.2	5.70
18	99.7	0.70	92.6	6.30	61.7	5.50
19	100	0.30	96.1	3.50	67.0	6.30
20	100	0	98.4	2.30	72.1	5.10
21	100	0	99.3	0.90	78.2	6.10
22	100	0	99.7	0.50	84.4	6.20
23	100	0	99.7	0	88.8	4.40
24	100	0	99.7	0	91.7	2.90

TABLE 2

200 mg Adinzolam Mesylate Tablets

	Example 4		Example 5		Example 6	
	15% Metolose 90SH-100		20% Metolose 90SH-100		30% Metolose 90SH-100	
(Hrs.) Time	% Dissolved	Rate	%Dissolved	Rate	%Dissolved	Rate
1	99.9	99.9	59.0	59.0	10.7	10.7
2	100	0	70.8	11.8	19.2	8.5
3	100	0	80.0	9.2	27.6	8.40
4	100	0	91.1	11.1	35.8	8.20
5	100	0	99.4	8.3	43.8	8.00
6	100	0	99.6	0.2	51.9	8.10
7	100	0	99.7	0.1	59.7	7.80
8	100	0	99.7	0	67.5	7.80
9	100	0	99.7	0	75.1	7.60
10	100	0	99.8	0.10	82.2	7.10
11	100	0	99.8	0	90.4	8.20
12	100	0	99.9	0.10	97.3	6.90
13	100	0	99.9	0	99.9	2.60
14	100	0	100	0	99.9	0
15	100	0	100	0	100	0.10
16	100	0	100	0	100	0
17	100	0	100	0	100	0
18	100	0	100	0	100	0
19	100	0	100	0	100	0
20	100	0	100	0	100	0
21	100	0	100	0	100	0
22	100	0	100	0	100	0
23	100	0	100	0	100	0
24	100	0	100	0	100	0

TABLE 2 (Cont'd.)

	Example 7		Example 8		Example 9	
	40% Metolose 90SH-100		50% Metolose 90SH-100		60% Metolose 90SH-100	
(Hrs.) Time	% Dissolved	Rate	%Dissolved	Rate	%Dissolved	Rate
1	8.21	8.21	5.89	5.89	5.29	5.29
2	15.4	7.19	10.5	4.61	9.16	3.87
3	21.6	6.20	14.6	4.10	12.6	3.44
4	27.4	5.80	18.6	3.90	16.1	3.50
5	33.0	5.60	22.3	3.80	18.8	2.70
6	38.8	5.80	26.0	3.70	21.8	3.00
7	44.0	5.20	29.7	3.70	24.7	2.90
8	49.2	5.20	33.5	3.80	27.5	2.80
9	54.6	5.40	37.4	3.90	30.6	3.10
10	60.3	5.70	41.3	3.90	33.6	3.00
11	66.4	6.10	45.5	4.20	36.7	3.10
12	72.7	6.30	49.9	4.40	39.9	3.20
13	80.5	7.80	54.8	4.90	43.1	3.20
14	88.2	7.70	60.0	5.20	46.4	3.30
15	94.5	6.30	65.5	5.50	49.8	3.40
16	98.2	3.70	71.4	5.90	53.5	3.70
17	99.7	1.50	77.7	6.30	57.2	3.70
18	100	0.30	83.4	5.70	60.5	3.30
19	100	0	88.6	5.20	64.6	4.10
20	100	0	93.1	4.50	68.9	4.30
21	100	0	96.1	3.00	72.7	3.88
22	100	0	98.2	2.1	76.7	4.00
23	100	0	98.2	0	80.3	3.60
24	100	0	100	1.8	--	--

TABLE 3

30 mg Adinazolam Mesylate Tablets

	Example 10		Example 11+		Example 12	
	90% Metolose 65SH-4000		44% Metolose 65SH-4000 35% Metolose SM-1500		45% Metolose 65SH-4000 45% Metolose SM-1500	
(Hrs.) Time	% Dissolved	Rate	%Dissolved	Rate	%Dissolved	Rate
1	8.87	8.87	11.1	11.1	10.7	10.7
2	14.2	5.33	16.8	5.70	16.7	6.00
3	18.6	4.40	21.3	4.50	21.6	4.90
4	22.4	3.80	26.0	4.70	26.4	4.80
5	26.1	3.70	29.8	3.80	31.3	4.90
6	29.3	3.20	34.0	4.20	36.3	5.00
7	32.4	3.10	38.2	4.20	41.9	5.60
8	35.2	2.80	43.2	5.20	48.8	6.90
9	38.2	3.00	48.7	5.50	57.1	8.30
10	41.7	3.50	56.0	7.30	67.9	10.8
11	46.1	4.40	66.4	10.4	89.9	22.0
12	51.2	5.10	76.8	10.4	99.0	9.90
13	58.6	7.40	93.1	16.3	100	1.00
14	64.5	5.90	96.3	3.20	100	0
15	70.4	5.90	97.8	1.50	100	0
16	76.8	6.40	98.9	1.10	100	0
17	84.5	7.70	99.6	0.70	100	0
18	93.6	9.10	—	—	—	—
19	98.9	5.30	—	—	—	—
20	99.7	0.80	—	—	—	—

+ Cumulative and differential plots (FIGURES 7 and 8)

TABLE 4

Dissolution Rate Data for 200 mg Flurbiprofen Tablets

(Hrs.)	Example 13		Example 14++		Example 15	
Time	% Dissolved	Rate	%Dissolved	Rate	%Dissolved	Rate
1	7.2	7.2	7.5	7.5	9.6	9.60
2	11.8	4.6	12.1	4.6	15.4	5.8
3	16.0	4.2	16.2	4.1	20.4	5.0
4	20.2	4.2	19.8	3.6	25.4	5.0
5	24.6	4.4	23.1	3.3	30.8	5.4
6	29.2	4.6	26.2	3.1	36.7	5.9
7	34.0	4.8	29.5	3.3	43.7	7.0
8	39.0	5.0	32.9	3.4	51.4	7.7
9	44.2	5.2	36.6	3.7	59.5	8.1
10	49.6	5.4	40.5	3.9	69.5	10
11	55.3	5.7	44.7	4.2	79.9	10.4
12	61.3	6.0	49.1	4.4	89.4	9.5
13	68.2	6.9	53.9	4.8	95.1	5.7
14	76.5	8.3	59.0	5.1	98.2	3.1
15	84.0	7.5	64.6	5.6	99.3	1.1
16	89.7	5.7	71.1	6.5	99.5	0.2
17	94.2	4.5	78.7	7.6	99.6	0.1
18	97.4	3.2	86.5	7.8	99.7	0.1
19	98.9	1.5	92.0	5.5	99.7	0
20	99.5	0.6	95.5	3.5	99.8	0.1
21	99.7	0.2	97.6	2.1	99.8	0
22	99.8	0.1	98.8	1.2	99.9	0.1
23	99.9	0.1	99.5	0.7	99.9	0
24	99.9	0	99.8	0.3	100	0

++ Cumulative and differential plots (FIGURES 9 and 10)

CLAIMS

1. A carrier base material combined with a therapeutically active medicament and shaped and compressed to a solid sustained release pharmaceutical dosage form having a bimodal release profile upon administration, carrier base material being one or more hydroxypropylmethylcelluloses and up to 50% by weight of the mixture of methylcellulose, sodium carbodymethylcellulose and/or other cellulose ether, and wherein at least one of the hydroxypropylmethylcelluloses, is a bimodal hydroxypropylmethylcellulose (B-HPMC) having a methoxy content of 19-30% by weight, a hydroxypropyl content of 4-12% by weight and an average molecular weight of 20,000-140,000.

2. A bimodal sustained release pharmaceutical formulation according to Claim 1 in which the carrier base material consists of one or more bimodal hydroxypropylmethylcelluloses selected from the group consisting of:

Metolose 60SH-4000,
Metolose 65SH-50,
Metolose 65SH-400,
Metolose 65SH-1500,
Metolose 65SH-4000,
Metolose 90SH-100,
Metolose 90SH-15000, or
Methocel F4-M.

3. A bimodal sustained release pharmaceutical formulation according to Claim 1 in which the therapeutically active medicament is selected from the group consisting of:

antihistamines, laxatives, vitamins, decongestants, gastrointestinal sedatives, anti-inflammatory substances, antacids, anti-infectives, coronary vasodilators, cerebral vasodilators, peripheral vasodilators, psychotropics, antimanics, stimulants, antidiarrheal preparations, antianginal drugs, vasoconstrictors, anticoagulants, antithrombotic drugs, analgesics, anti-pyretics, hypnotics, sediatives, anti-emetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants,

mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, anti-asthmatics, expectorants, cough suppressents, mucolytics and antiuricemic drugs.

4. A bimodal sustained release pharmaceutical formulation according to Claim 1 in which the therapeutically active medicament is flurbiprofen.

5. A bimodal sustained release pharmaceutical formulation according to Claim 1 in which the therapeutically active medicament is adinazolam or a pharmaceutically acceptable salt thereof.

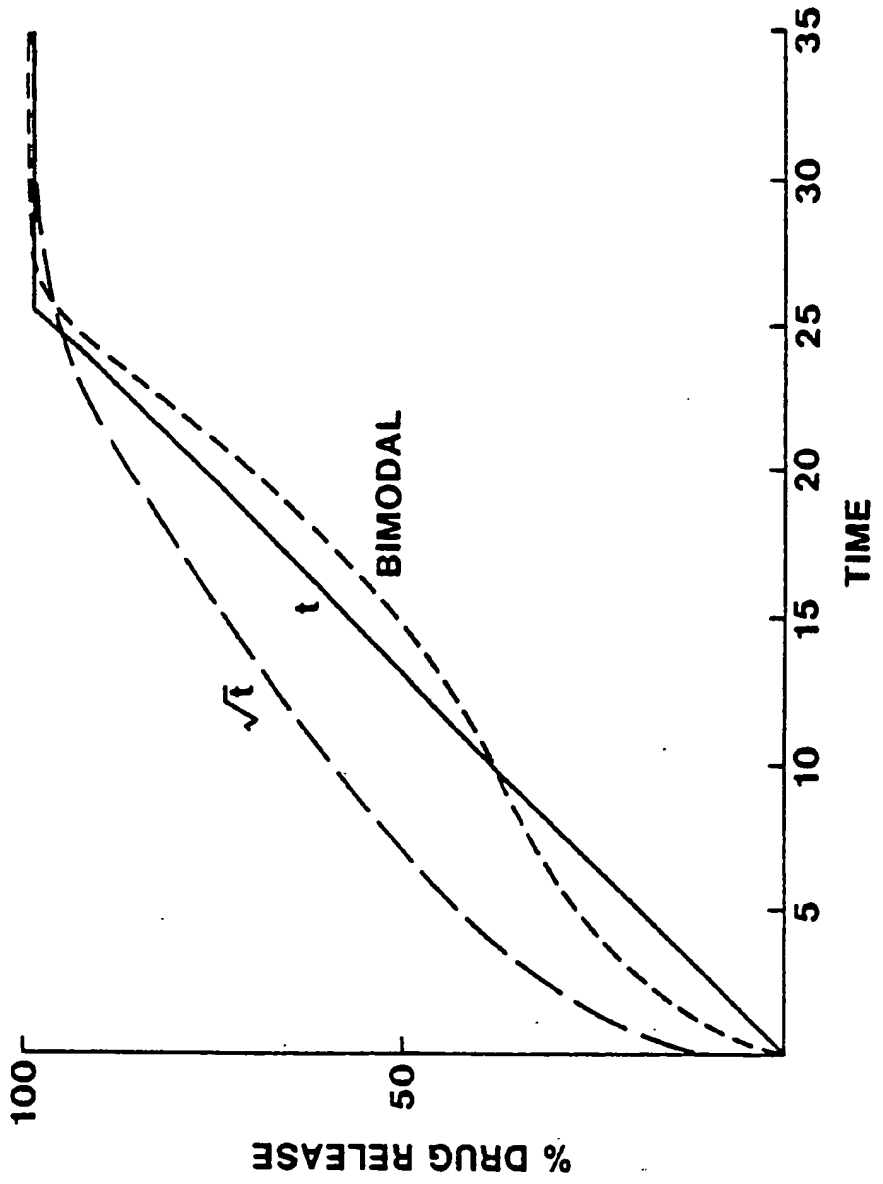
6. A bimodal sustained release pharmaceutical formulation according to Claim 1 in which the therapeutically active medicament is adinazolam mesylate.

7. A bimodal sustained release pharmaceutical formulation according to Claim 1 in which the therapeutically active medicament is an anti-inflammatory drug selected from the group consisting of ibuprofen, flurbiprofen, diclofenac, indomethacin, naproxen or naproxen sodium.

8. A method for the preparation of a bimodal sustained release pharmaceutical formulation containing a therapeutically active medicament and having a bimodal release profile upon administration, consisting of compressing and shaping a mixture of a therapeutically active medicament and a carrier base material consisting of one or more hydroxypropyl-methylcelluloses and up to 50% by weight of the mixture of methylcellulose, sodium carbodymethylcellulose and/or other cellulose ether, and wherein at least one of the hydroxypropylmethylcelluloses, is a bimodal hydroxy-propylmethylcellulose (B-HPMC) having a methoxy content of 19-30% by weight, a hydroxypropyl content of 4-12% by weight and an average molecular weight of 20,000-140,000.

Figure 1

COMPARISON OF BIMODAL RELEASE
WITH CONSTANT AND DECLINING RELEASE PROFILES



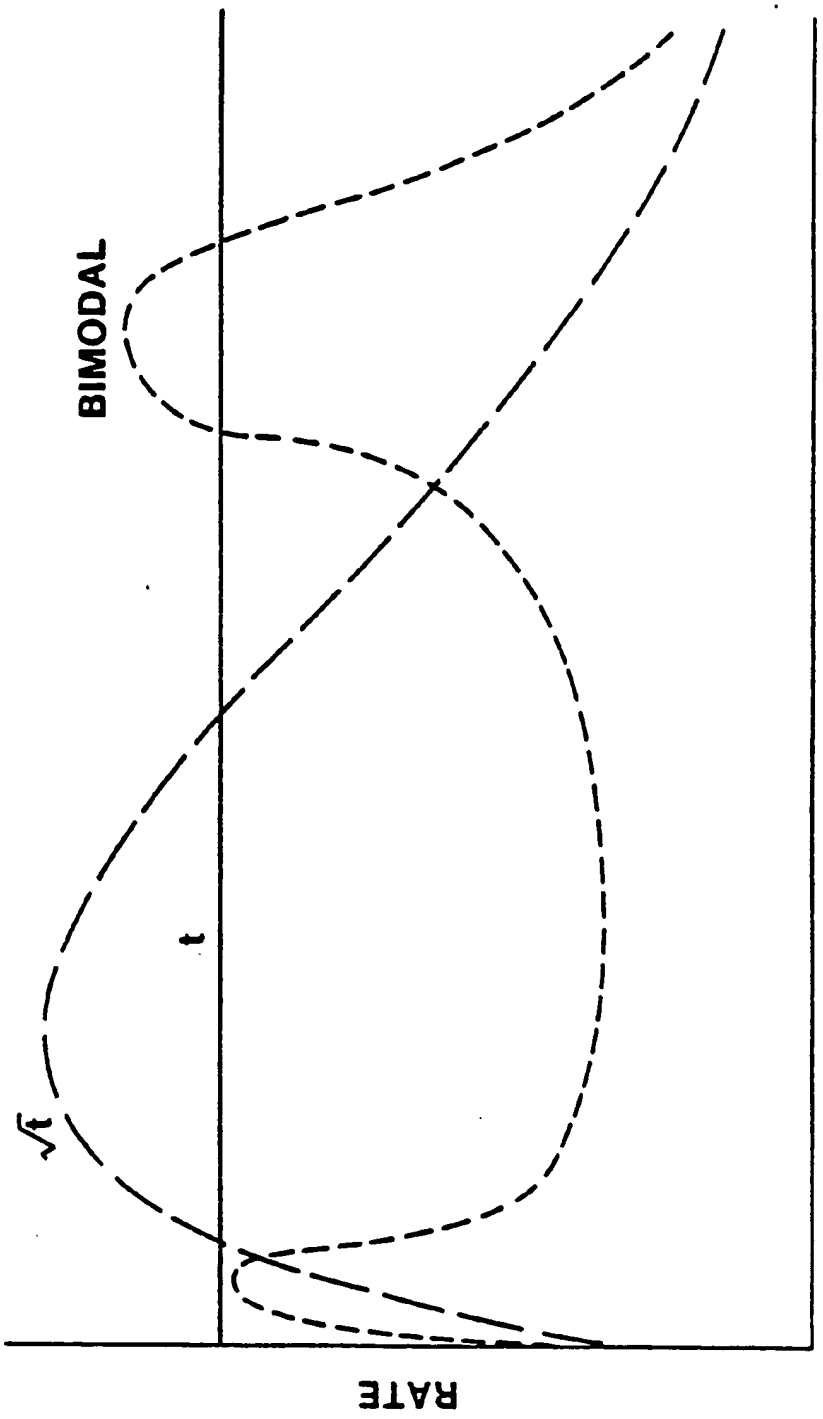


Figure 2

COMPARISON OF BIMODAL RATE OF RELEASE
WITH CONSTANT AND DECLINING RATES OF RELEASE

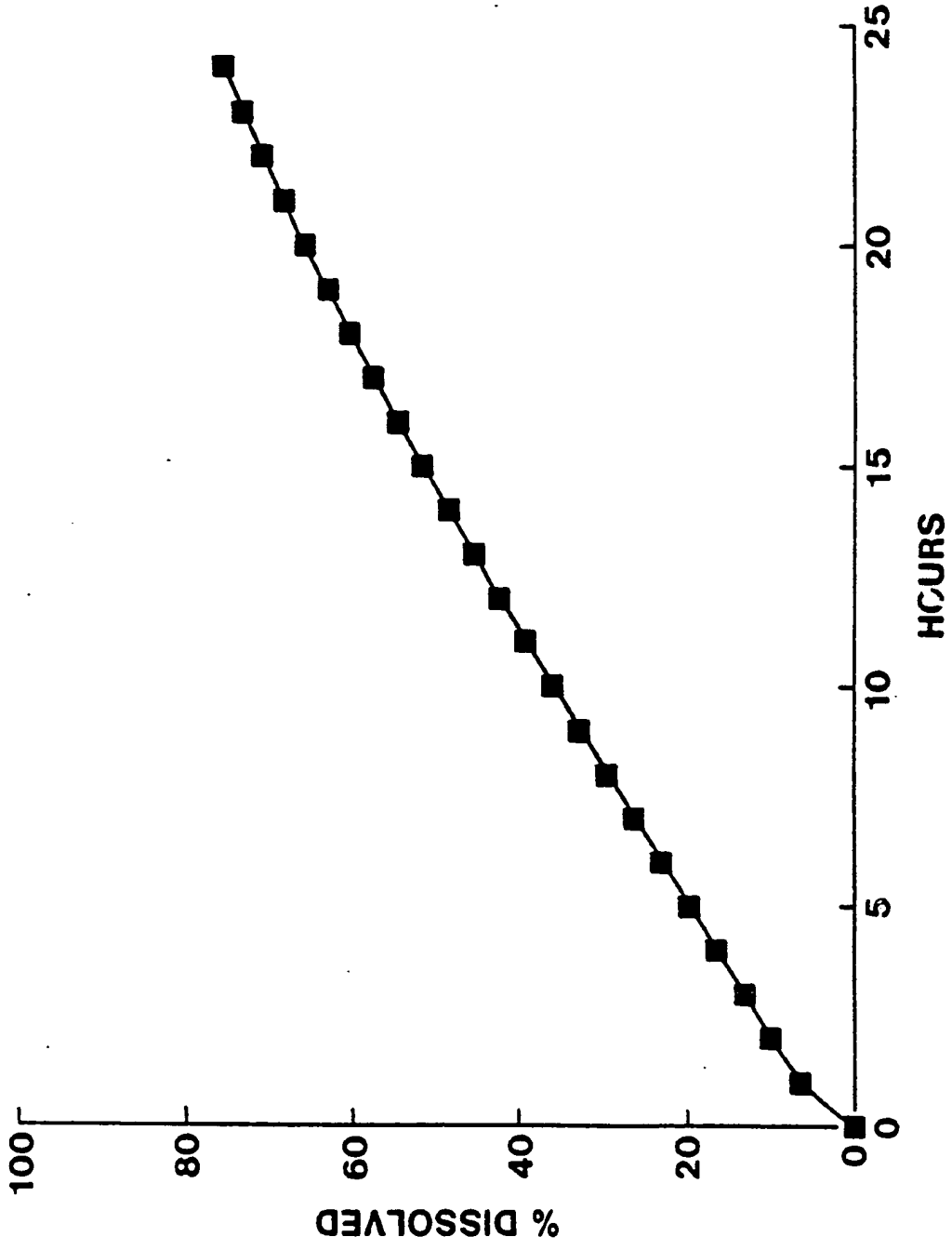


Figure 3

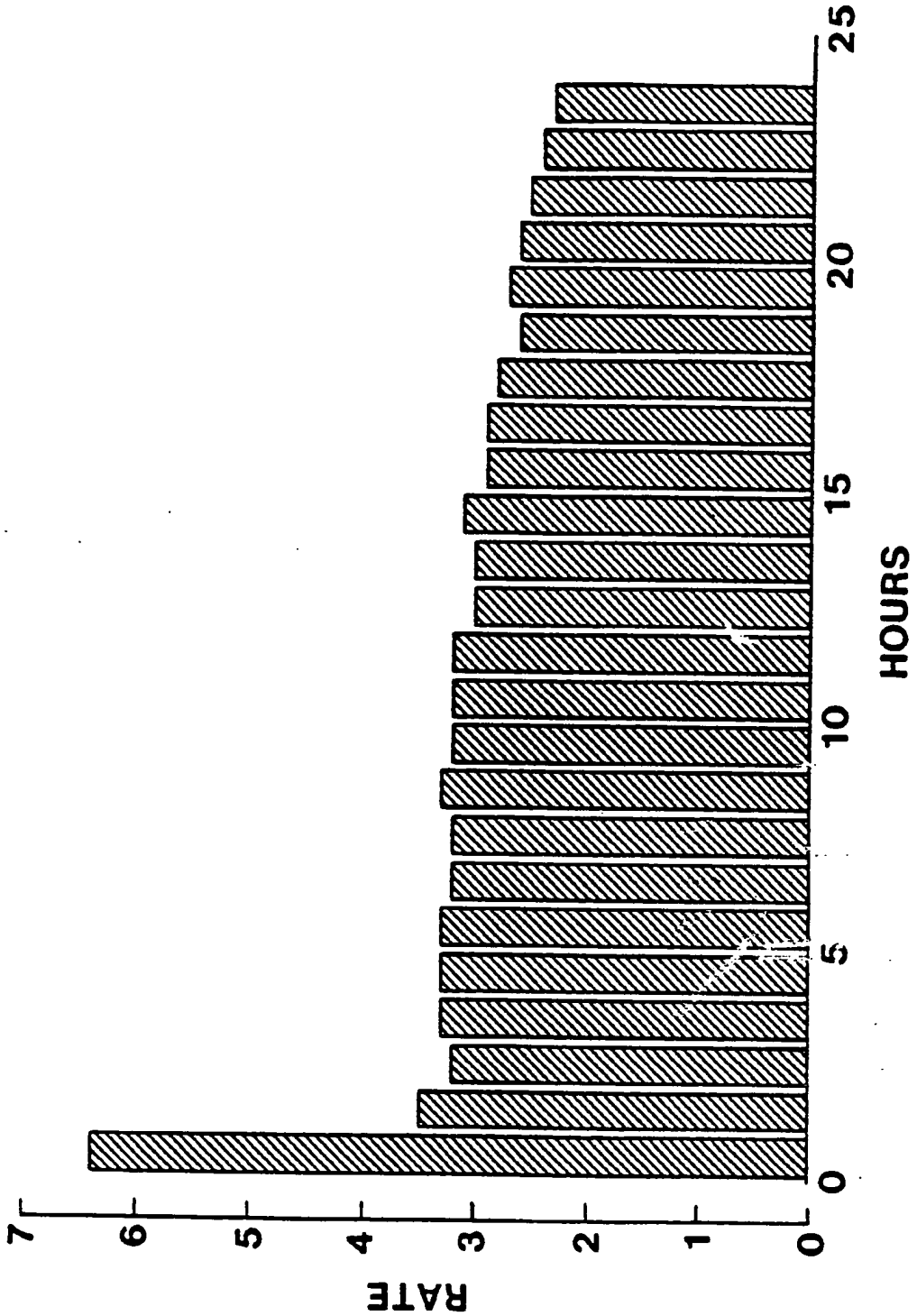


Figure 4

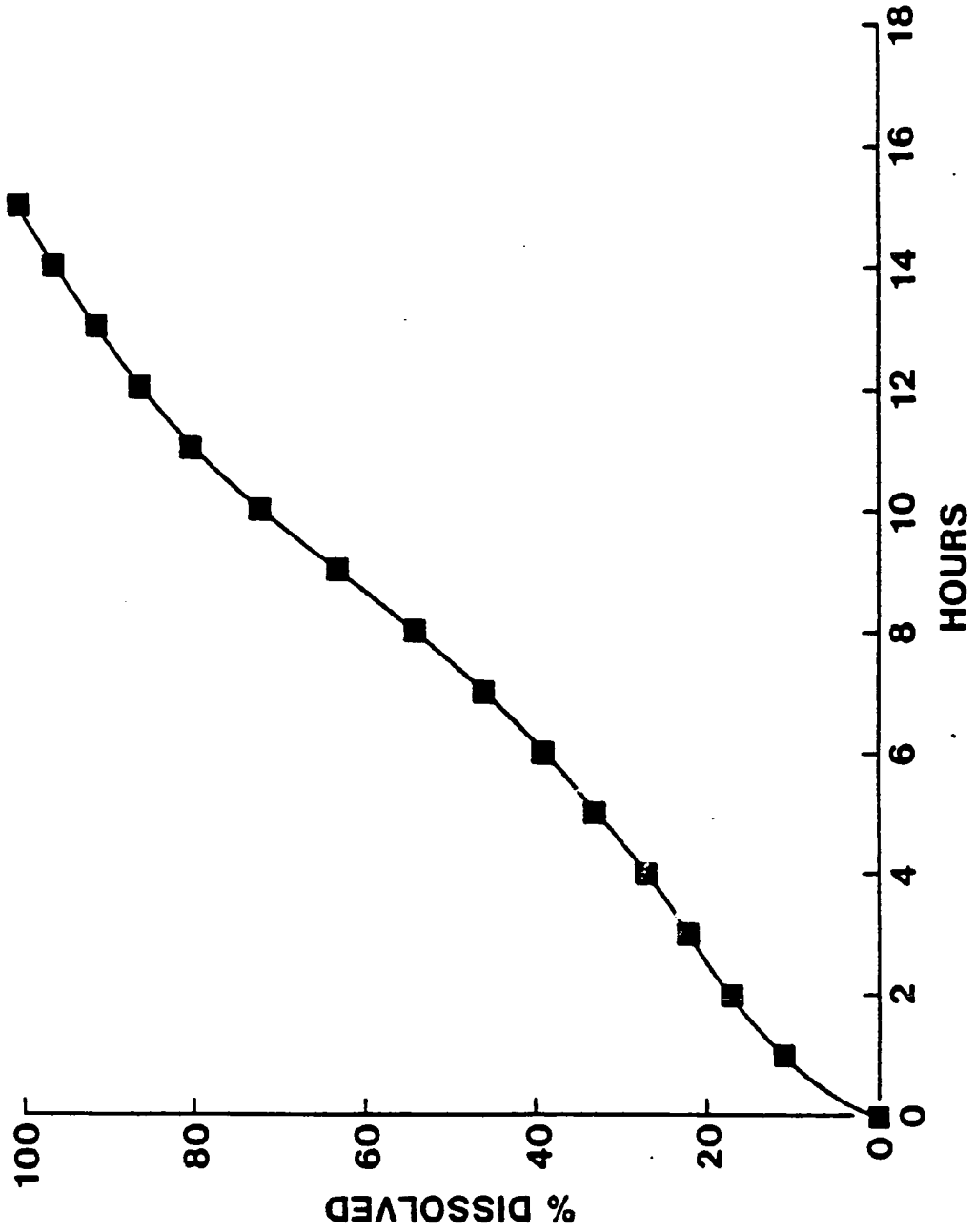


Figure 5

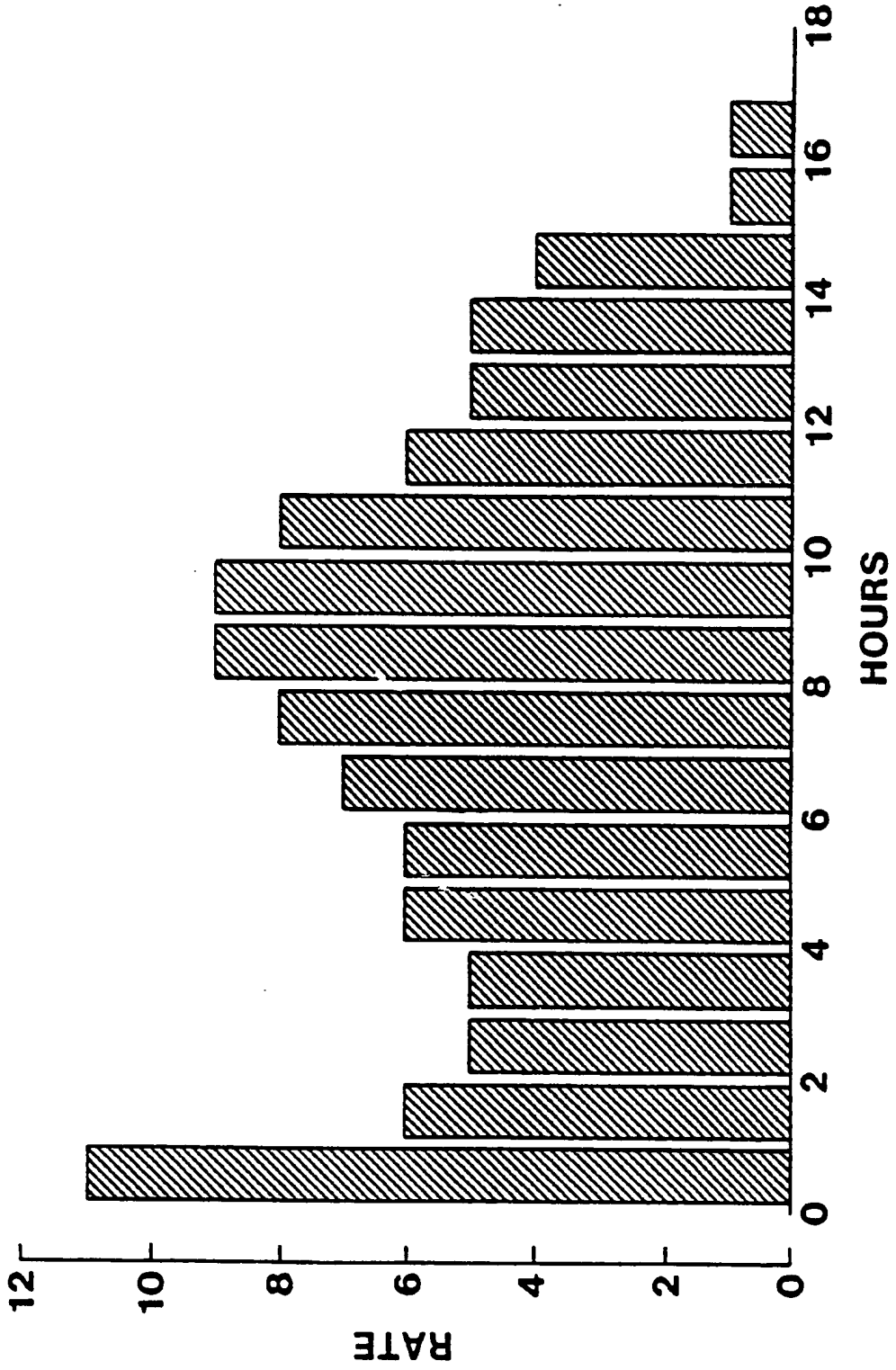


Figure 6

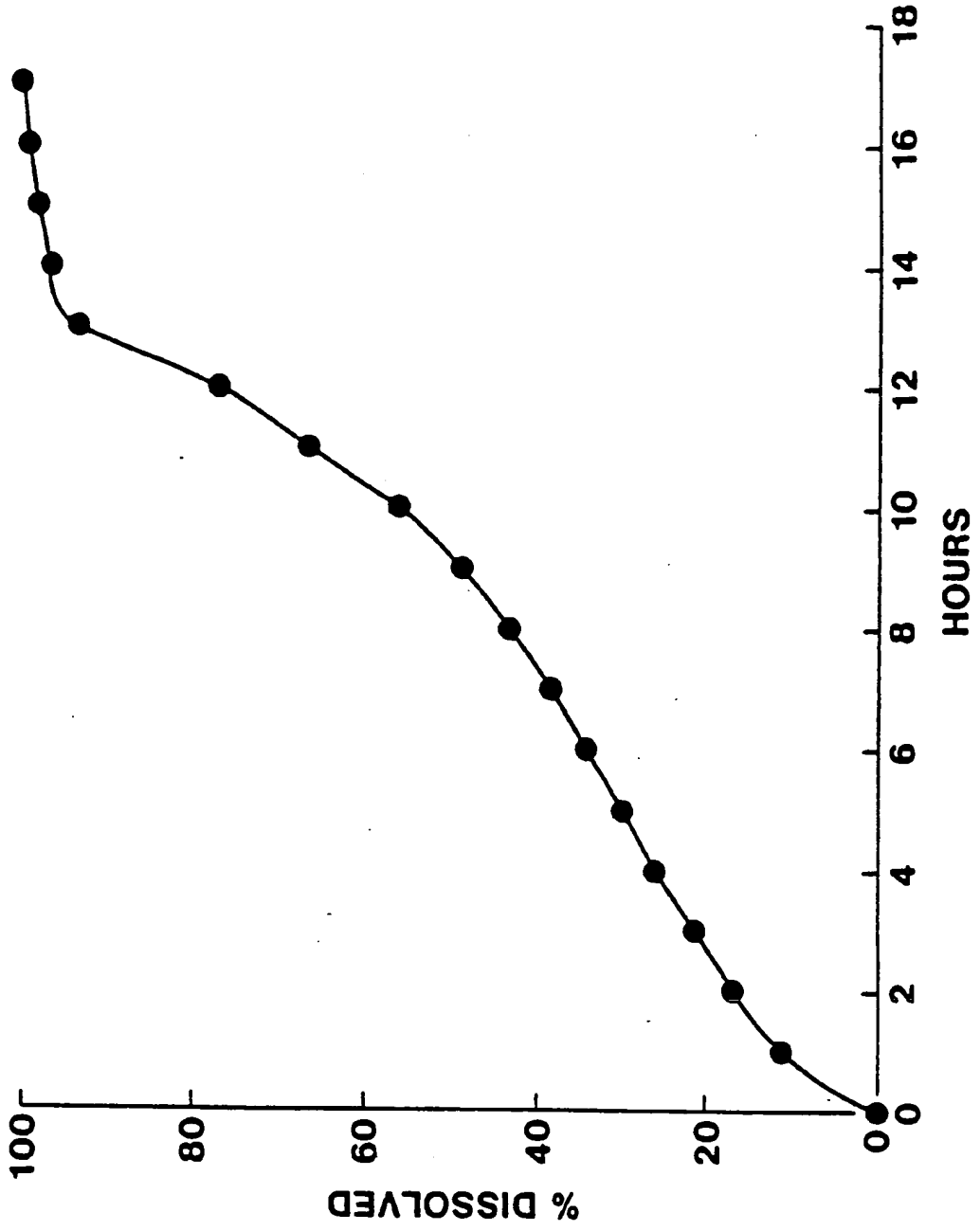


Figure 7

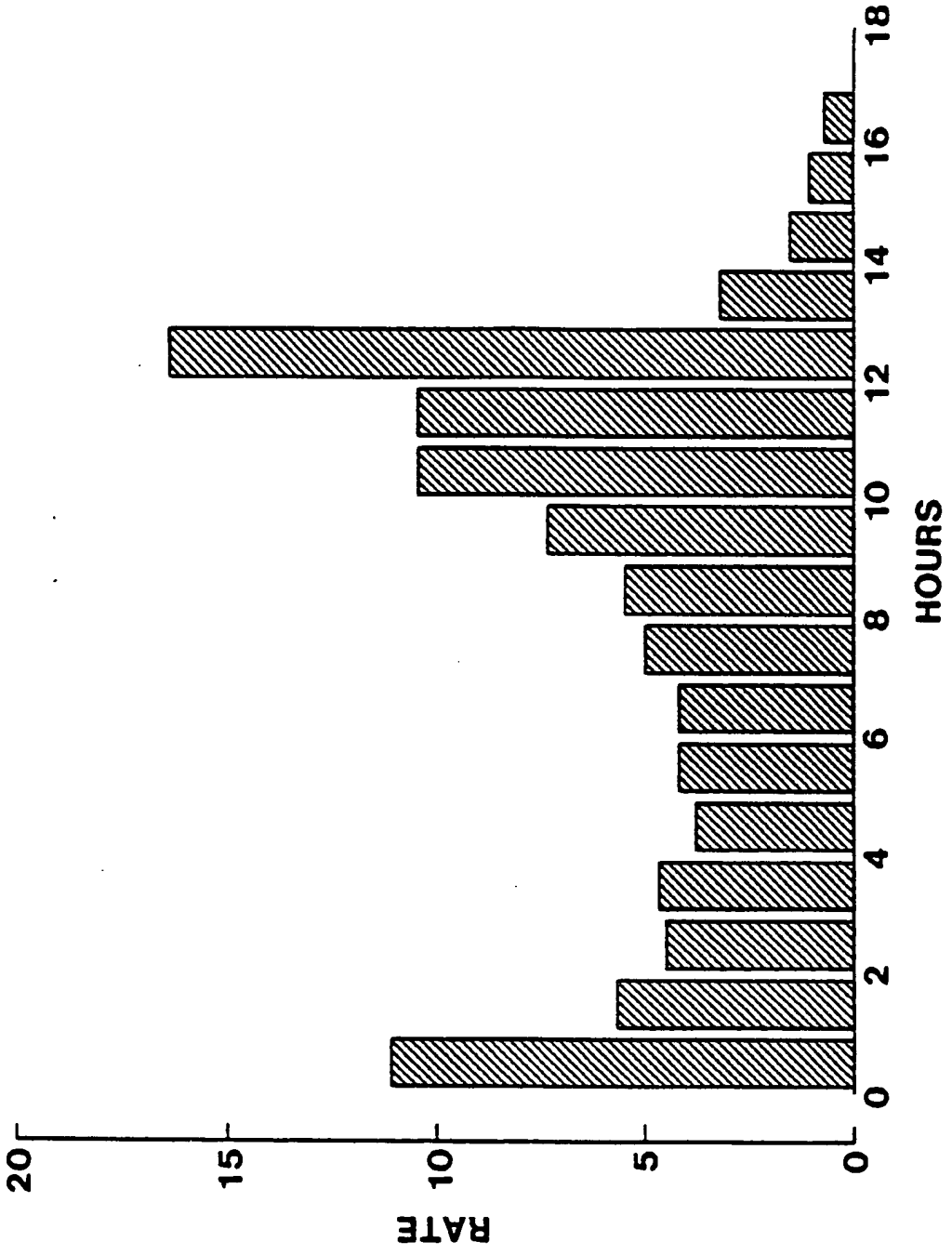


Figure 8

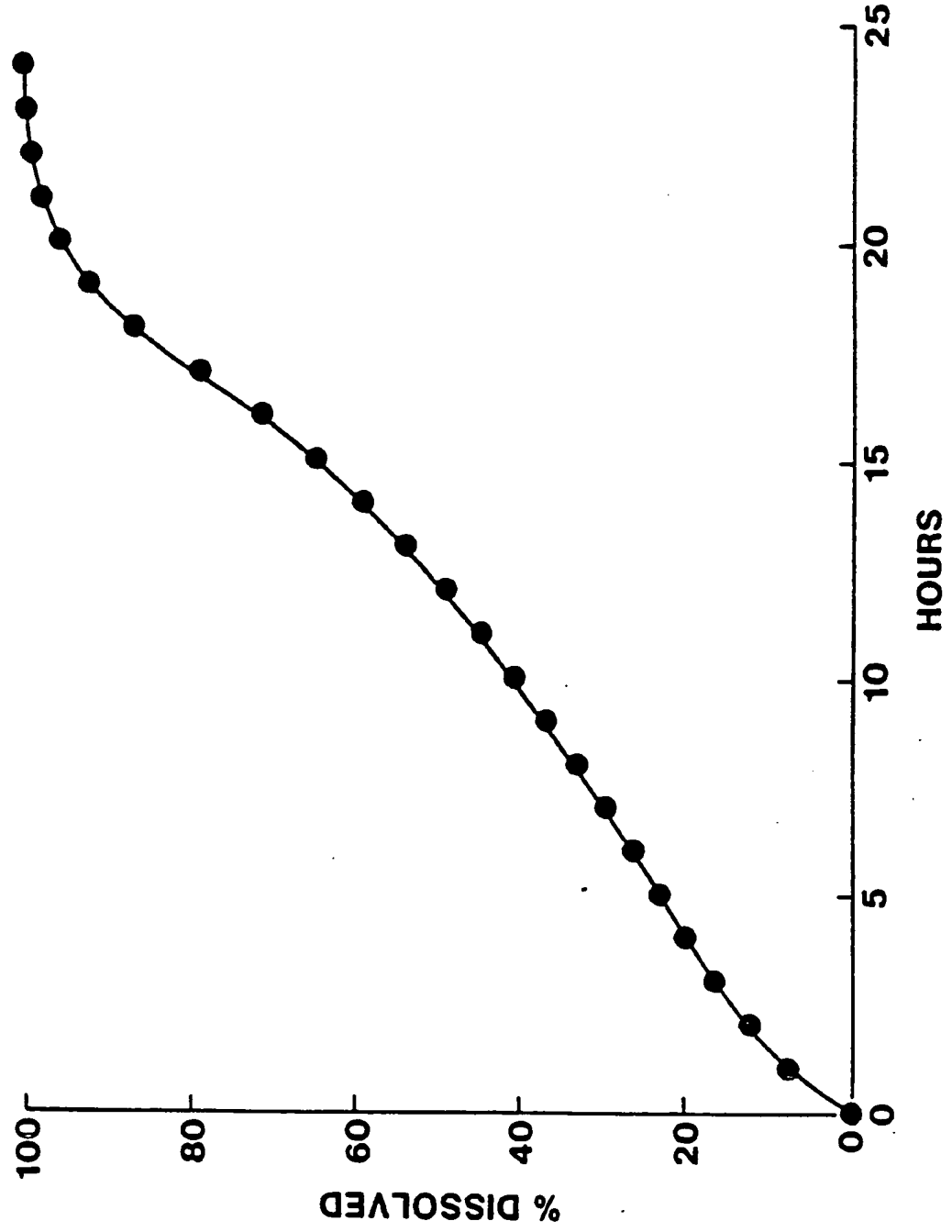


Figure 9

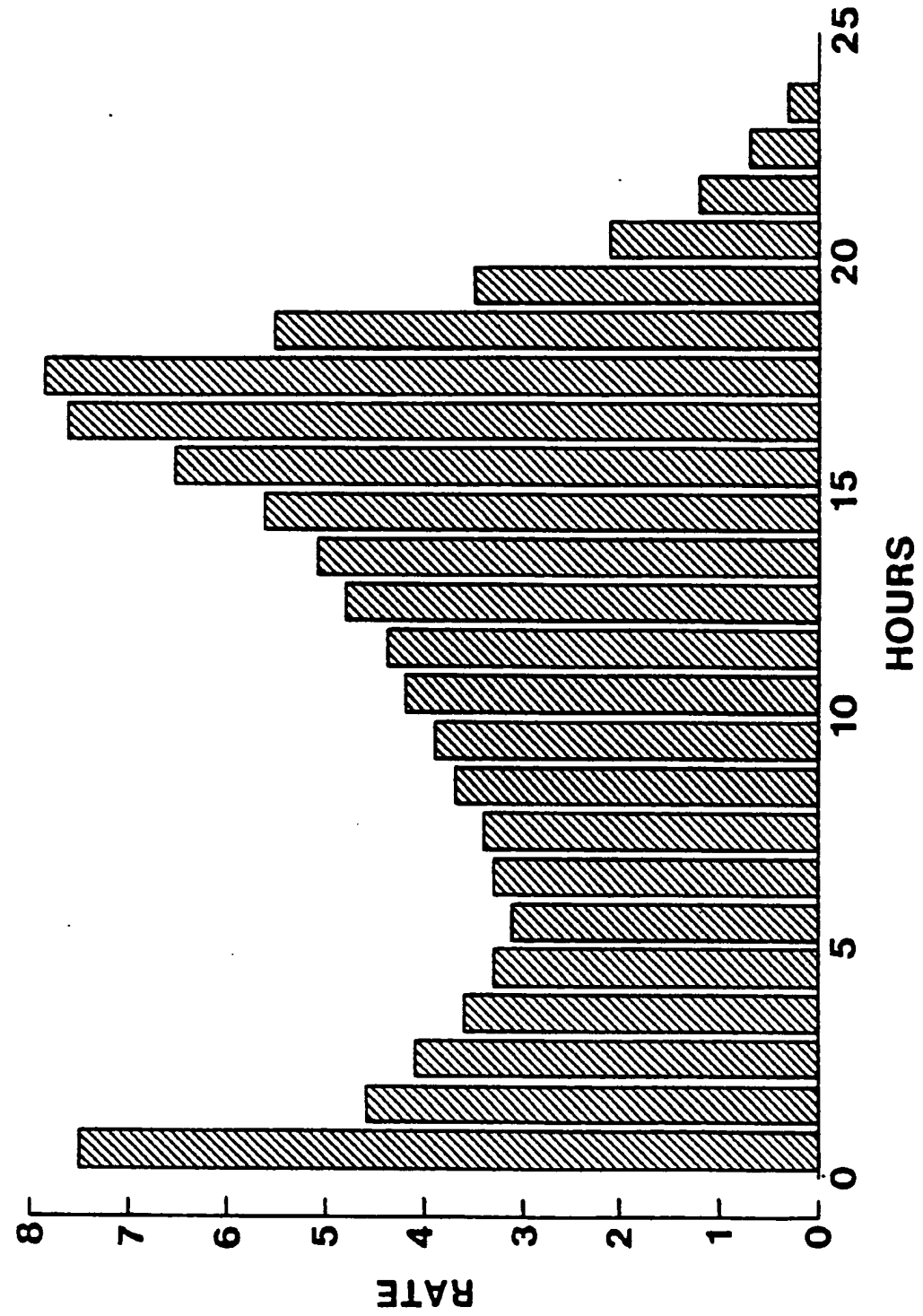


Figure 10

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 86/01360

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/22

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US, A, 4389393 (J.M. SCHOR) 21 June 1983, see column 4, lines 7-28, lines 47-65; claims 1-22 cited in the application	1-8
A	US, A, 4369172 (J.M. SCHOR) 18 January 1983, see column 3, lines 1-14; column 5, line 61 - column 7, line 21; claims cited in the application	1-8
A	US, A, 4167558 (P.R SHETH) 11 September 1979, see column 4, lines 2-11; claims cited in the application	1-8

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1 September 1986	10 OCT 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 86/01360 (SA 13811)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/10/86

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4389393	21/06/83	BE-A-	896136	01/07/83
		GB-A-	2117239	12/10/83
		FR-A,B	2523845	30/09/83
		NL-A-	8301042	17/10/83
		SE-A-	8301579	27/09/83
		JP-A-	58174311	13/10/83
		DE-A-	3309516	01/12/83
		CA-A-	1188614	11/06/85
		CH-B-	655241	15/04/86
US-A- 4369172	18/01/83	BE-A-	895391	15/04/83
		SE-A-	8207167	19/06/83
		GB-A,B	2111386	06/07/83
		FR-A,B	2518409	24/06/83
		DE-A,C	3246492	30/06/83
		JP-A-	58110513	01/07/83
		NL-A-	8204893	18/07/83
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		CA-A-	1195929	29/10/85
US-A- 4167558	11/09/79	None		